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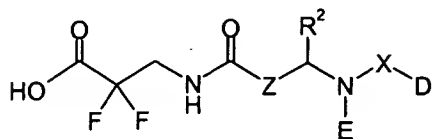
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CLAIMS

1. A compound of the general formula (I):



(I)

wherein

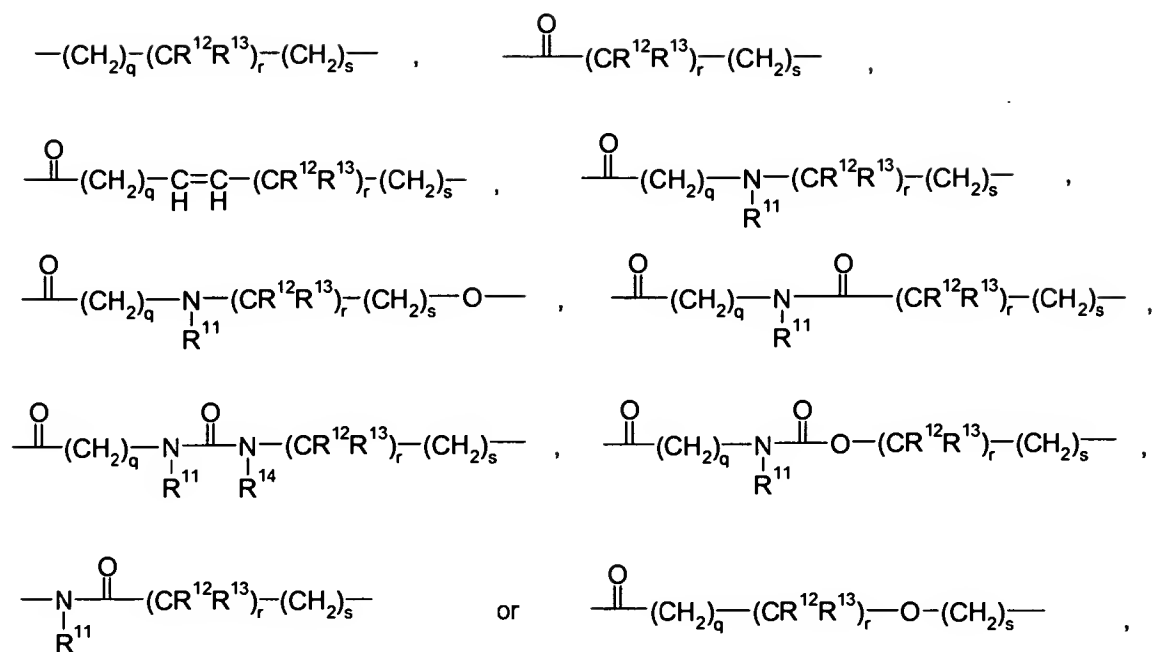
R^2 is hydrogen or C_{1-6} -alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, - CF_3 , - OCF_3 , - NO_2 , - OR^9 , - NR^9R^{10} and C_{1-6} -alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6} -alkyl,

X is



5 wherein

r is 0 or 1,

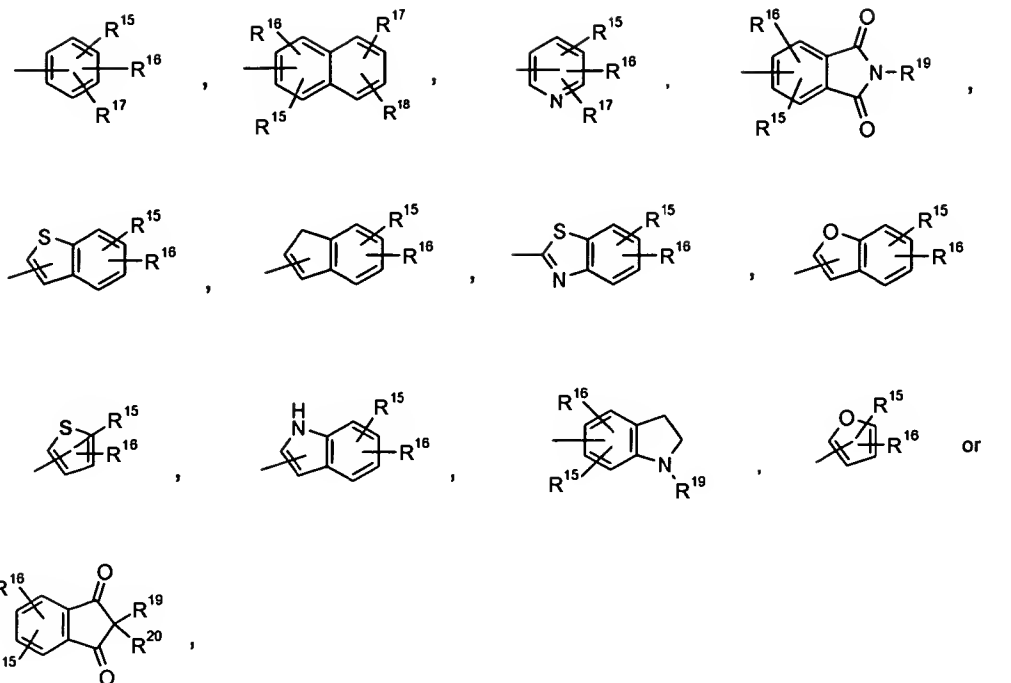
q and s independently are 0, 1, 2 or 3,

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R¹¹, R¹², R¹³ and R¹⁴ independently are hydrogen or C₁₋₆-alkyl,

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= 4464
1095660

D is



5 wherein

R^{15} , R^{16} , R^{17} and R^{18} independently are

- 10
- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

- 15 • C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR²¹, -NR²¹R²² and C₁₋₆-alkyl,

- 20 • C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio,

C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR²¹, -NR²¹R²² and C₁₋₆-alkyl,

wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl or aryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁵ to R¹⁸ when placed in adjacent positions together may form a bridge -(CR²³R²⁴)_a-O-(CR²⁵R²⁶)_c-O-,

wherein

a is 0, 1 or 2,

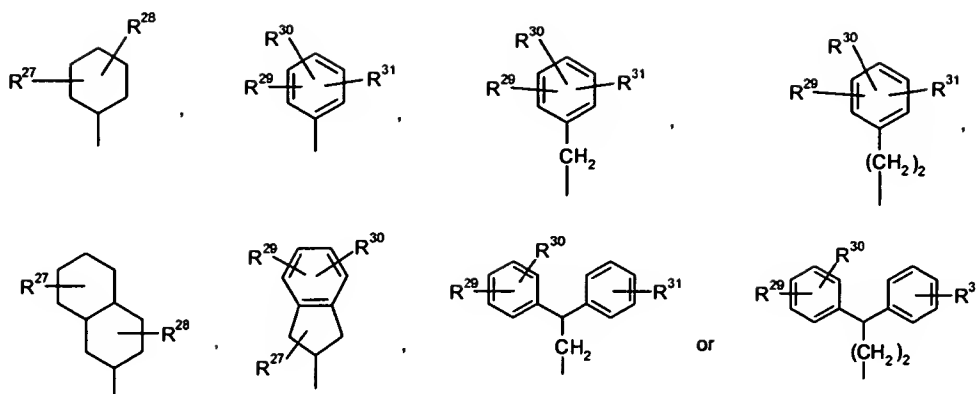
c is 1 or 2,

R²³, R²⁴, R²⁵ and R²⁶ independently are hydrogen, C₁₋₆-alkyl or fluorine,

R¹⁹ and R²⁰ independently are hydrogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

70

E is



wherein

5

 R^{27} and R^{28} independently are

hydrogen, halogen, -CN, -CF₃, -OCF₃, -OR³², -NR³²R³³, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl or aryl,

10

wherein the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³², -NR³²R³³ and C₁₋₆-alkyl,

wherein

15

 R^{32} and R^{33} independently are hydrogen or C₁₋₆-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

20

 R^{29} , R^{30} and R^{31} independently are

25

- hydrogen, halogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁴, -NR³⁴R³⁵, -SR³⁴, -S(O)R³⁴, -S(O)₂R³⁴, -C(O)NR³⁴R³⁵, -OC(O)NR³⁴R³⁵, -NR³⁴C(O)R³⁵, -OCH₂C(O)NR³⁴R³⁵, -C(O)R³⁴ or -C(O)OR³⁴,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

- C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

wherein R³⁴ and R³⁵ independently are hydrogen, C₁₋₆-alkyl or aryl,

or R³⁴ and R³⁵ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R²⁹, R³⁰ and R³¹ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_l-CR³⁶R³⁷-(CH₂)_l-O-, -(CH₂)_l-CR³⁶R³⁷-(CH₂)_l- or -S-(CH₂)_l-CR³⁶R³⁷-(CH₂)_l-S-,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

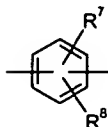
R³⁶ and R³⁷ independently are hydrogen or C₁₋₆-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R² is hydrogen.

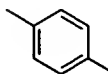
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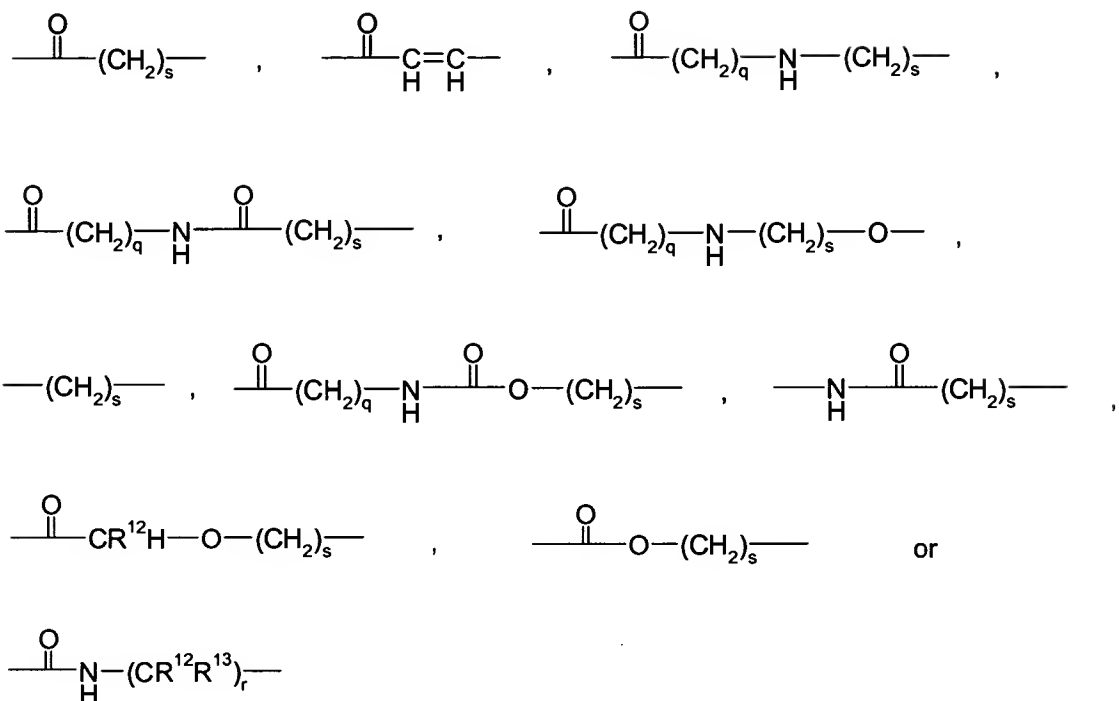
3. A compound according to claim 1, wherein Z is



10 wherein R^7 and R^8 are as defined in claim 1.

4. A compound according to claim 3, wherein Z is

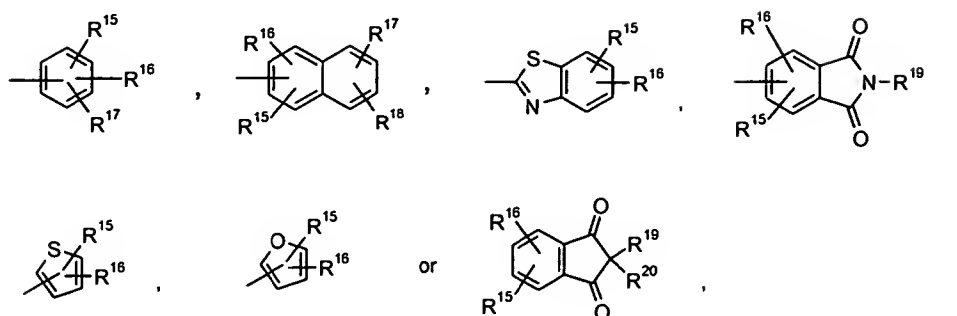
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- 5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl.
6. A compound according to claim 5, wherein X is -C(O)NH-, -C(O)NHCH₂-,
-C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -C(O)CH=CH-, -(CH₂)_s-, -C(O)-, -C(O)O-
10 or -NHC(O)-, wherein s is 0 or 1.
7. A compound according to claim 6, wherein X is -C(O)NH-, -C(O)NHCH₂-,
-C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -CH₂-, -C(O)- or -NHC(O)-.
- 15 8. A compound according to claim 7, wherein X is -C(O)NH-.

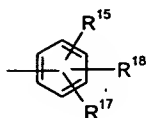
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9. A compound according to claim 1, wherein D is



5 wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} and R^{20} are as defined in claim 1.

10. A compound according to claim 9, wherein D is



10

wherein R^{15} , R^{16} and R^{17} are as defined in claim 1.

11. A compound according to claim 9, wherein R^{15} , R^{16} and R^{17} independently are hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, $\overline{\text{SCF}}_3$, C₁₋₆-alkyl, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹,
 15 -C(O)R²¹, -CH₂OR²¹, -C(O)NR²¹R²², -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C₃₋₈-cycloalkyl or aryl, or two of the groups R^{15} , R^{16} and R^{17} when placed in adjacent positions together form a bridge $-(\text{CR}^{23}\text{R}^{24})_a\text{-O-(CR}^{25}\text{R}^{26})_c\text{-O-}$, wherein R^{21} and R^{22} independently are hydrogen or C₁₋₆-alkyl, and a, c, R^{23} , R^{24} , R^{25} and R^{26} are as defined in claim 1.

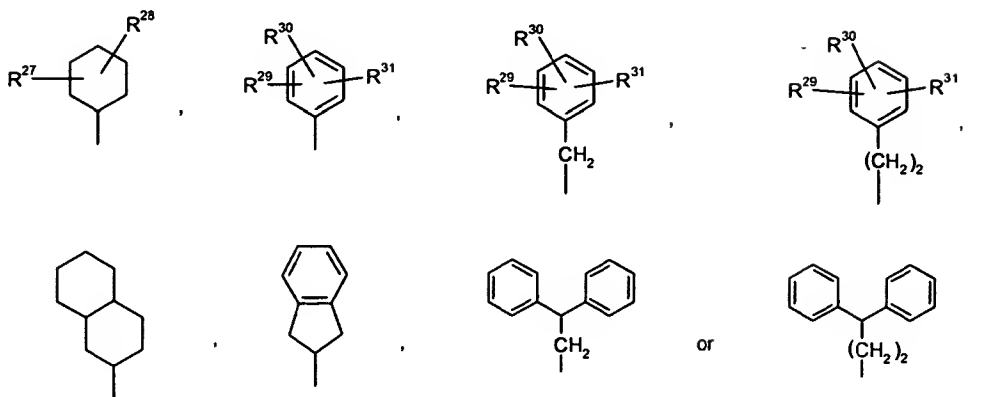
20 12. A compound according to claim 11, wherein R^{15} , R^{16} and R^{17} independently are hydrogen, halogen, -CN, -CF₃, -OCF₃ or C₁₋₆-alkoxy.

13. A compound according to claim 12, wherein R^{15} , R^{16} and R^{17} independently are hydrogen, halogen, -CF₃ or -OCF₃.

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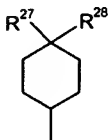
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14. A compound according to claim 1, wherein E is



5 wherein R^{27} , R^{28} , R^{29} , R^{30} and R^{31} are as defined in claim 1.

15. A compound according to claim 14, wherein E is



10

wherein R^{27} and R^{28} are as defined in claim 1.

16. A compound according to claim 14, wherein R^{27} and R^{28} independently are

- 15
- hydrogen, C_{1-6} -alkyl,
 - C_{3-8} -cycloalkyl, C_{4-8} -cycloalkenyl or phenyl, which may optionally be substituted as defined in claim 1.

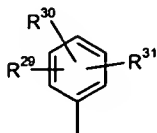
20 17. A compound according to claim 16, wherein R^{27} is hydrogen and R^{28} is

- C_{1-6} -alkyl,

- C₄₋₈-cycloalkenyl or C₃₋₈-cycloalkyl, which may optionally be substituted as defined in claim 1.

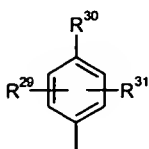
18. A compound according to claim 14, wherein E is

5



wherein R²⁹, R³⁰ and R³¹ are as defined in claim 1.

10 19. A compound according to claim 18, wherein E is



wherein R²⁹, R³⁰ and R³¹ are as defined in claim 1.

15

20. A compound according to claim 18, wherein R²⁹, R³⁰ and R³¹ independently are

20

- hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁴, -NR³⁴R³⁵, -SR³⁴, -S(O)R³⁴, -S(O)₂R³⁴, -C(O)NR³⁴R³⁵, -OC(O)NR³⁴R³⁵, -NR³⁴C(O)R³⁵, -OCH₂C(O)NR³⁴R³⁵, -C(O)R³⁴ or -C(O)OR³⁴,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

25

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

- C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

30

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6} -alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said
nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing
one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and
optionally containing one or two double bonds.

21. A compound according to claim 20, wherein R^{29} , R^{30} and R^{31} independently are

hydrogen, C_{1-6} -alkoxy, $-CF_3$, $-OCF_3$ or $-NR^{34}R^{35}$, wherein R^{34} and R^{35} are as defined in claim
1, or

C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl, which are optionally substituted as defined in
claim 1.

22. A compound according to claim 21, wherein R^{29} , R^{30} and R^{31} independently are

hydrogen or

C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl, which are optionally substituted as defined in
claim 1.

23. A compound according to claim 22, wherein R^{29} , R^{30} and R^{31} independently are hydro-

gen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl, wherein C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl
are optionally substituted with C_{1-6} -alkyl.

24. A compound according to claim 23, wherein R^{29} and R^{31} are both hydrogen and R^{30} is

C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl, wherein C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl are
optionally substituted with C_{1-6} -alkyl.

25. A compound according to claim 24, wherein R^{29} and R^{31} are both hydrogen and R^{30} is

C_{1-6} -alkyl.

26. A compound according to claim 25, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{4-8} -cycloalkenyl which is optionally substituted with C_{1-6} -alkyl.

27. A compound according to claim 1, wherein said compound has an IC_{50} value of no greater than $5\text{ }\mu\text{M}$ as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

28. A compound according to claim 27, wherein said compound has an IC_{50} value of less than $1\text{ }\mu\text{M}$, preferably of less than 500 nM and even more preferred of less than 100 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

29. A compound according to claim 1, wherein said compound is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, impaired glucose tolerance, Type 2 diabetes, Type 1 diabetes and obesity.

30. A compound according to any one of the claims 1 to 29 for use as a medicament.

31. A pharmaceutical composition comprising at least one compound according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

32. A pharmaceutical composition according to claim 31 in unit dosage form, said composition comprising from about 0.05 mg to about 1000 mg of the compound according to claim 1.

33. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

34. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

35. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of hyperglycemia.

36. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for lowering blood glucose in a mammal.

37. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of IGT.

38. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

39. Use according to claim 38 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

40. Use according to claim 38 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

41. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

42. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of obesity.

43. Use according to any one of the claims 33 to 42 in a regimen which comprises treatment with a further antidiabetic agent.

44. Use according to any one of the claims 33 to 43 in a regimen which comprises treatment with a further antiobesity agent.

45. Use according to any one of the claims 33 to 44 in a regimen which additionally comprises treatment with an antihypertensive agent.

46. A method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

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47. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg per day.

5 48. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.1 mg to about 1000 mg per day.

49. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.5 mg to about 500 mg per day.

10 50. A method for the treatment and/or prevention of glucagon-mediated disorders and diseases, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

15 51. A method for the treatment and/or prevention of hyperglycemia, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

20 52. A method for lowering blood glucose in a mammal, said method comprising administering to said mammal in need thereof an effective amount of a compound according to claim 1.

25 53. A method for the treatment and/or prevention of impaired glucose tolerance, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

54. A method for the treatment and/or prevention of Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

30 55. A method for delaying or preventing the progression from impaired glucose tolerance to Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

56. A method for delaying or preventing the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

5 57. A method for the treatment and/or prevention of Type 1 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

58. A method for the treatment and/or prevention of obesity, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

59. The method according to claim 46, further comprising administering an antidiabetic agent to said subject.

15 60. The method according to claim 46, further comprising administering an antiobesity agent to said subject.

61. The method according to claim 46, further comprising administering an antihypertensive agent to said subject.

20 62. A pharmaceutical composition according to claim 31 in unit dosage form, said composition comprising from about 0.1 mg to about 500 mg of the compound according to claim 1.

25 63. A pharmaceutical composition according to claim 31 in unit dosage form, said composition comprising from about 0.5 mg to about 200 mg of the compound according to claim 1.

30 64. A compound according to claim 27, wherein said compound has an IC_{50} value of less than 500 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

35 65. A compound according to claim 27, wherein said compound has an IC_{50} value of less than 100 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).